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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
SPECTOR, L	
ART UNIT	**PAPER NUMBER**
1812	17

18N2/1016

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DATE MAILED: 10/16/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6/9/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-11, 13, 20, 22-24, 27-36, 38-41 are pending in the application.
   Of the above, claims 1-9, 29-31, 35, 36, 38-41 are withdrawn from consideration.
2. ☒ Claims 12, 14, 15-19, 21, 25, 26, 37 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 10, 11, 13, 20, 22-24, 27, 28, 32, 33 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-11, 13, 20, 22-24, 27-36, 38-41 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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...CTION

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election of Invention II, Claims 10, 11, 13, 20, 22-24, 27, 28, 32 and 33 in Paper No. 14, submitted July 6, 1995 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts, compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. The abstract is not sufficiently descriptive, as it does not refer to either thrombopoietin or MPL-ligand, and thus does not sufficiently identify the invention. Complete revision of the content of the abstract is required on a separate sheet.

The cross-reference to related applications, which appears at the first page of the specification, should be updated to reflect the current pendency status of all applications to which reference is made.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 22, 24, 28, 32 and 33 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited in scope to expression vectors and processes for the expression of thrombopoietin (TPO) in eukaryotic cells. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification discloses at page 18 that TPO is expected to be highly glycosylated, and further indicates that "experimental evidence indicates that the carbohydrate associated with the second domain is involved in proper intracellular assembly and secretion of the protein during its biosynthesis." In view of this admission, it is extremely unpredictable that TPO would, when recombinantly expressed in a prokaryotic cell, be capable of proper intracellular assembly. This is because prokaryotic cells are widely recognized in the art to be incapable of protein glycosylation, which applicants have indicated is expected to be essential for proper assembly (folding?) of the protein. Therefore, enablement is not commensurate in scope with claims to expression vectors and processes for the expression of TPO in prokaryotic cells.

Claims 10, 11, 13, 20, 22-24, 27, 28, 32 and 33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 20, as well as the claims dependent from them, are indefinite with respect to "80% identical". This phrase has unambiguous meaning when it is applied to the comparison of two sequences of equal length. However, sequences of unequal length are evidently considered to be comparable by this standard. If gaps are required to optimally align the two sequences, how is the gap to be assessed in determining identity? The ambiguity is best shown by example: consider the two sequences, ABCDEF and ABEF. These could be compared in any of four ways:

```
ABCDEF      4/6 = 67%          ABCDEF      2/6 = 33%
|| | |                        ||
AB--EF      4/4 = 100%         ABEF        2/4 = 50%
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The claims can *only* be considered definite if comparisons of "sequence identity" are confined to sequences of identical length.

Claim 23 is indefinite as it is not the secretory signal sequence itself which would be operably linked to the DNA segment, but rather a DNA segment *encoding* a secretory signal sequence. In addition, in line 3 of the claim, as well as of claim 24, "the" should more properly read --said--.

Prior Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Methia (Blood 82:1395, submitted by applicants) suggests that *mpl* is a cytokine receptor for a thrombopoietic cytokine and suggests using the receptor to clone the ligand.

Skoda (EMBO 12:2645, submitted by applicants) indicates that as of 1993 it was still unknown whether *mpl* had a ligand binding domain, or alternatively required a heterologous protein to form or supply the ligand binding domain.

Mignotte et al. (Genomics 20:5), published March 1, 1994 (after the filing date of the current invention) disclose the cloning and sequence of the human c-*mpl* gene (the *mpl* receptor).

The following patents are cited to establish the state of the art for various proteins which are designated by various terms recognized by the art as being synonymous with *mpl* ligand, none of which appear to be the same as encoded by the currently claimed nucleic acids. All are disclosed as being useful for the treatment of thrombocytopenia:

U.S. Patent Number 4,894,440 (Rosenberg) discloses purified megakaryocyte-colony stimulating factor (Meg-CSF), a human protein with M_R=15,000 which can be bound and eluted from WGA-Sepharose (see Col. 2). In the paragraph bridging columns 2-3, the inventors suggest cloning the Meg-CSF and propose a protocol for doing so.

U.S. Patent Number 5,326,558 (Turner et al.) discloses a human megakaryocytopoietic factor purified from urine and then cloned. The sequences do not correspond to those of the instant specification.

U.S. Patent Number 5,260,417 (Grant et al.) disclose a megakaryocyte growth promoting activity which is a 45 kD protein.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette D. Draper, can be reached at (703)308-4232.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the Examiner at the telephone number above when a fax is being transmitted.

Lorraine Spector

Lorraine Spector, Ph.D.
Patent Examiner

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